OXIDATIVE STRESS IN CHRONIC RENAL DISEASES

Thesis

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بسم الله الرحمن الرحيم
وَقُـــــل رَّبِّ زِدْنِـــــي
عِلْمـــًا
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Dedication
To:
My Dear Parents
Who gave me too much
and received too little
My Wife (Dr Heba)
and My Lovely Sons
Fatema & Abd El Monaem
My Real Friend Dr. Helmy
Ahmed

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LIST OF ABBREVIATIONS

Abbrev.	Meaning
ALA :	Alpha lipoic acid**.**
ALS:	Amyotrophic lateral sclerosis.
ATP :	Adenosine triphosphate.
CKD:	Chronic kidney disease.
CRP:	C reactive protein.
Cu Zn SOD:	Copper and zinc containing dismutase.
DHLA:	Dihydrolipoic acid.
DM:	Diabetes mellitus.
DNA:	Deoxy nucleic acid.
ESR :	Erythrocyte sedimentation rate.
ESRD:	End stage renal disease.
Fe SOD:	Iron containing dismutase.
GRF:	Glomerular filtration rate.
GSH:	Glutathione.
GSSG:	Glutathione disulfide.
GT:	Granulocyte transfusion.
HD:	Haemodialysis .
HDL:	High density lipoproteins.
Health ABS study:	Health, Aging and Body composition study.
HIV:	Human immune deficiency virus.
HMG-COA:	3-hydroxy-3 methyl –glutaryl COA.
HNE	4-hydroxy-2-nonenal.
JNC.7:	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High blood pressure.
LDL:	Low density lipoproteins.
LDL-OX:	Oxidized Low density lipoproteins.
MDRD:	Modification of Diet in Renal Diseases.

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Meaning
Mn SOD:	Manganese containing dismutase.
MPO:	Myeloperoxidase .
NAD:	Nicotinamide adenine dinucleotide.
NHAES III:	The Third National Health and Examination Surgery.
Ni SOD:	Nickel containing dismutase.
NKF :	National kidney foundation .
NKFB:	Nuclear factor KB .
NMDA:	N-methyl D-aspartic acid.
NO:	Nitric oxide.
O_2^-:	Super oxide.
OH :	Hydroxyl group.
$ONOO^-$:	Preoxynitrite.
PD:	peritoneal dialysis.
PKD :	Polycystic kidney disease.
PMNs:	Polymorph nuclear leucocytes.
RBCs:	Red blood corpuscles .
RNA:	Ribonucleic acid.
ROS:	Reactive oxygen species.
RRT:	Renal replacement therapy.
SLE:	systemic lupus erythrematosus.
SOD:	Super oxide dismutase.
TGFB:	Transforming growth factor B.
US :	United States**.**
USRDS :	United State renal data system.
WBCs :	White blood corpuscles .

INTRODUCTION

Chronic kidney diseases CKD are defined as glomerular filtration rate of less than 60 ml/min/1.73 m^2 of body surface, ***(Kao et al, 2010).*** Progressive renal disease is characterized by the development of glomerulosclerosis and interstitial fibosis. The final common pathway predicts the degree of renal dysfunction and long term prognosis for almost all forms of CKD, ***(Nogues et al., 2010).*** The worldwide incidence of kidney failure is on the rise and the treatment is costly, thus the global burden of the illness is growing. The kidney failure patients require either a kidney transplant or dialysis. Alternative dialysis modalities are haemodialysis (HD) or peritoneal dialysis (PD) ***(Paul et al., 2008)***. *Internationally*: The incidence rates of end stage renal disease (ESRD) have increased steadily internationally since 1989. The united state has the highest incident rate of ESRD followed by Japan. Japan has the highest prevalence per million population, with the united states taking second place, ***(Verrli, 2006).*** A specially designed questionare was used to explore the predominart trends of pre-end stage renal failure in Egypt. According to the most recent Egyptian registry data, 75.1 new patients per million population were accepted into the different renal replacement therapy programs in the last year ***(Barsoum, 2002).*** This is admittedly an under estimate, since the response rate of renal replacement therapy "RRT" centers to registry questionnaire is still meager. An

earlier estimate based on the counting the deaths attributed to end stage renal disease before RRT was introduced into the country was 192 per million population ***(Barsoum, 2002).*** The prevalence of pre-dialysis renal sufficiency would grossly amount to 100.000 patients ***(Barosum, 2002)***.

Oxidative stress is defined as an imbalance in the generation of reactive oxygen species "ROS" and plays a major role in disease pathogenesis ***(Ciselle et al., 2009).*** The potential role of oxidative processes in the development of various diseases "degenerative diseases, neoplasms" has been discussed in several publication ***(Siekmeier et al., 2007).*** ROS and nitrogen species are produced by the metabolism of normal cells ***(Palbo, 2009).*** ROS may be admitted to the organism (e.g by cigarette smoking or by the environment) or may be released from different cells in various diseases (e.g diabetes mellitus and end stage renal disease), ***(Siekeimer, et al., 2007).*** In the course of chronic kidney disease CKD, a chronic inflammatory state develops whichis characterized by oxidative stress and sustained monocycte activities ***(Gausson et al., 2005).*** Myeloperoxidase "MPO" is aleucocytic enzyme and is a proinflammatory molecules implicated in the promotion and propagation of atherosclerosis. Indeed, when secreted by activated leucocyte at sites of inflammation ***(Georgorio, 2007)*** MPO, is one of such active substances which is a constituent of azurophilic granules of polymorph nuclear leucocytes that oxidizes chloride ions to the potent bactericidal oxidant hybochlorous acid ***(Cinthia et al., 2009).***

MPO is a critical inflammatory mediator at which stimulates endothelial apoptosis, induces endothelial dysfunction and increase plaque vulnerability, thus contributing to development of ischemia ***(Hui et al., 2009).***

Antioxidant is any substance that when present at low concentrations compared with that of an oxidizable substrate, scientifically delays or inhibits oxidation of the substrate. This definition includes compounds of non-enzymatic as well as enzymatic nature ***(Aggarwal et al., 2009)***. The antioxidant defense systems are of major importance because pre-oxidative damage is currently regarded as one of the most important cause of impaired body functions ***(John et al., 2008)***.Humans have evolved a high sophisticated and complex antioxidant protection system. It involves a variety of components, both exogenous and endogenous in origin, that function interactively and synergistically to neutralize free radicals, ***(Jacob, 1995)***. Renal disease patients especially those at end stage with their dietary restriction of fresh fruits and vegetables have lower level of vitamin C. Each haenodyalisis session include oxidative stress, with ROS being generated on the surface of dialysis membrane by the activation of polymorphoculear neutrophils due to bioincomptability, while causing concomitant loss of antioxidant vitamins through the dialysis process itself ***(Kao et al., 2010).***

AIM OF THE WORK

The aim of the present study is to determine the role of oxidative stress in the pathogenesis and severity of chronic renal disease.